Fever of Unknown Origin

Kathleen Ryan, MD, MPH*

KEYWORDS

• FUO • Fever of unknown origin • PUO • Prolonged fever

KEY POINTS

- A thorough history and physical examination is critical for identifying etiology of a fever of unknown origin (FUO).
- Causes of FUO in adolescents are broad and most commonly include infectious etiology, although autoimmune, connective tissue disorders, other inflammatory processes and malignancy are among the more than 200 etiologies.
- Connective tissue disorders and autoimmune disorders are more frequent causes of FUO in adolescents than in children .
- Classic FUO occuring in healthy adolescents without "red flag" symptoms with a normal physical exam and initial lab work up, and a negative diagnostic work up is reassuring for eventual resolution without sequel.

INTRODUCTION

Definition

Fever of unknown origin (FUO) has been recognized as a disease state for over 100 years. The first commonly accepted definition of FUO was published in 1961 and included (1) fever greater than 101° F (38.3° C) on multiple occasions (2) at least 3 week duration of fever (3) without identifiable cause despite at least a 1 week inpatient evaluation.[1] Overtime, this definition was considered both too rigid and too ill defined. Given the impracticality of prolonged hospitalizations and advancing technology for diagnosis, the duration of work up was shortened to 3 days inpatient evaluation and/or 3 outpatient clinic visits.[2]

Multiple sources suggest that all time requirements regarding the duration of evaluation be eliminated and instead FUO should be defined as a fever lacking known etiology after completing a minimum work up.[3–5] Additionally, the recommended minimum duration of fever to meet the definition of "FUO" has been decreased. Some studies suggest a minimum duration of 14 days of fevers to be considered in evaluations of FUO.[6–8] Other studies suggested that evaluation for "FUO" can begin in as little as 5 to 7 days of fever in pediatric patients.[8–10] Starting evaluation at shorter

Infectious Disease, Department of Pediatric, Medical College of Wisconsin & Children's Hospital of Wisconsin, Suite C450, 999 North 92 nd Street, Wauwatosa, WI 53226, USA
* Corresponding author.
E-mail address: ktryan@mcw.edu

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duration is also appropriate in certain patient populations (see Considerations later in discussion).

Given the heterogeneity of the etiology of FUO, individualized approach to patients with FUO has always been recommended. Although this personalized approach allows for more tailored care, the lack of consistency in diagnostic criteria does present problems when attempting to define the prevalence, shifting dynamics of etiology, and following outcomes for FUO on a population level.

Incidence

Fevers of unknown origin occur worldwide to people of all ages. As noted above, inconsistencies in inclusion criteria over time and geographic location limits the generalizability of any study results. The limited data that exists demonstrated FUO accounts for almost 3% of hospital admissions in adults.[11] Additional data suggests an incidence of 0.5% to 3% of hospital admission in pediatric patients are a result of FUOs.[8,12] Studies demonstrate adolescents make up approximately 20% to 25% of all pediatric patients with FUO.[6,10]

Although different studies have shown varying incidence of gender predominance, two different systemic reviews of adults with FUO have indicated there may be, at most, a slight increase incidence of male over females (55% males and 50% females).[13,14] Single site studies from both US and Korea also found an increase incidence in males (53%–65%) overall in the pediatric population as well.[6,10,15] The subset of patients ultimately found to have connective tissue disorders are predominantly female.[6]

Nature of the problem

Fevers of unknown origin (FUO) are caused by over 200 different etiologies.[16] (**Table 1**). The etiology of FUO can be subdivided into four major etiologic subcategories including (1) infectious, (2) non-infectious inflammatory or autoimmune disorders (sometimes only including connective tissue disorders) (3) malignancy and (4) other. Overall, an increasing proportion of FUO fall into a fifth category in which no etiology is ever found.

The relative incidence of different etiologic subgroups of FUO vary throughout the world. Locations in Asia had three to four times greater rate of infectious causes for FUO compared to Europe.[13] In comparison, centers in Europe found a significantly higher relative incidence of “no etiology ever found” in FUO cases. Presumably, the increased availability of rapid diagnostic testing resulted in the establishment of diagnosis in patient who would have previously been identified as FUO by 14 to 21 days.[13]

Historically, infectious etiologies have been the predominant cause of FUO in both children and adults throughout the world. When comparing studies by similar authors over time, the incidence of infectious causes has decreased over time.[11,13,14] This is presumably also related to faster diagnosis of many of these infectious etiology,[17] although decreasing rates of many previously common infectious agents can also be contributing to these results. FUO in children (including adolescents) have even higher relative rates of infectious etiology than adults. Relative rates of infectious triggers of pediatric FUO vary widely in studies (17%–50%)[6,8] while infectious causes of FUO in adults ranges closer to 15% to 35%.[5]

Within the US, a single site study of pediatric FUO reported viral etiology in almost 9% of cases caused by agents including Epstein Barr virus, cytomegalovirus, other herpes viruses, metapneumovirus, and enterovirus. Bacterial infections were often localized infections (septic arthritis, gluteal abscess, parapneumonic effusion, intraabdominal infection, endocarditis). Specific bacterial pathogens identified included

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Table 1
Causes of fever of unknown origin (FUO)

Infectious

- Abscesses
  - Abdominal
  - Brain
  - Dental
  - Hepatic
  - Paraspinal
  - Pelvic
  - Perinephric
  - Rectal
  - Retroperitoneal
  - Subphrenic
  - Psoas
  - Infected urachal cyst
  - Vertebral
- Viruses
  - Adenovirus
  - Arborviruses
  - Cytomegalovirus
  - Epstein-Barr virus
  - Hanta Virus
  - Hepatitis viruses
  - HIV
  - Human picornavirus
- Fungal diseases
  - Blastomycosis (extrapulmonary)
  - Coccidioidomycosis (disseminated)
  - Histoplasmosis (disseminated)
- Bacterial diseases
  - Actinomycosis
  - Bartonella henselae (cat-scratch)
  - Brucellosis
  - Campylobacter
  - Chlamydia
  - Francisella tularensis (tularemia)
  - Listeria monocytogenes (listeriosis)
  - Meningococcemia (chronic)
  - Mycobacterium (non-tuberculosis)
  - Mycoplasma pneumoniae
  - Neisseria meningitis (chronic)
  - Rat-bite fever (Streptobacillus moniliformis)
  - Salmonella
  - Tuberculosis
  - Whipple disease
  - Yersiniosis
  - Tuberculosis
- Localized infections
  - Cholangitis
  - Infective endocarditis
  - Lymphogranuloma venereum
  - Mastoiditis
  - Osteomyelitis
  - Pneumonia
  - Pyelonephritis
  - Psittacosis
  - Sinusitis
- Rickettsiae
  - African tick-bite fever
  - Anaplasmosis
  - Ehrlichia canis
  - Ehrlichiosis (E chaffeensis, E ewingii)
  - Q fever (Coxiella burnetii)
  - Rocky Mountain spotted fever
  - Tick-borne typhus
- Spirochetes
  - Borrelia burgdorferi (Lyme disease)
  - Relapsing fever (Borrelia recurrentis)
  - Leptospirosis
  - Rat-bite fever (Spirillum minus)
  - Syphilis
- Parasitic diseases
  - Amebiasis
  - Babesiosis
  - Giardiasis
  - Leishmania
  - Malaria
  - Toxoplasmosis
  - Trichinosis
  - Trypanosomiasis
  - Visceral larva migrans (Toxocara canis/cati)

Non-Infectious Immune-Mediated Diseases

- Rheumatologic diseases
  - Autoimmune cholangitis
  - Aortitis
  - Behçet disease
  - Juvenile dermatomyositis
  - Juvenile idiopathic arthritis
  - Rheumatic fever
  - Sjögren syndrome
  - Systemic lupus erythematosus
  - Polyarteritis nodosa
- Miscellaneous inflammatory
  - Hemophagocytic syndromes
  - Kawasaki disease
  - Kikuchi-Fujimoto disease
  - Immunoblastic lymphadenopathy
  - Löfgren syndrome
  - Periodic fever syndromes
  - Schnitzler syndrome
  - Subacute necrotizing lymphadenitis
- Granulomatous diseases
  - Granulomatosis with polyangiitis
  - Crohn disease
  - Granulomatous colitis
  - Granulomatous hepatitis
  - Granulomatous peritonitis
  - Sarcoidosis
  - Ulcerative colitis
  - Vasculitis syndrome

(*continued on next page*)

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Table 1
(*continued*)

Malignancies		
Hodgkin disease	Atrial myxoma	Cholesterol granuloma
Non-Hodgkin's Lymphoma	Hepatocellular carcinoma	Inflammatory pseudotumor
Leukemia	Neuroblastoma	Pheochromocytoma
Wilms tumor	Other solid tumor malignancies	Lymphomatoid granulomatosis
		Myeloproliferative syndromes

Other		
Hypersensitivity diseases	Miscellaneous	Miscellaneous (continued)
Drug fever	Addison disease	Paroxysmal hemoglobinurias
Hype eosinophilic syndrome	Castleman disease	Pericarditis
Hypersensitivity pneumonitis	Chronic active hepatitis	Poisoning
Serum sickness	Cyclic neutropenia	Postpericardiotomy syndrome
Weber-Christian disease	Diabetes insipidus (central and nephrogenic)	Pulmonary embolism
Familial & Hereditary	Drug fever	Resorbing hematoma
Anhidrotic ectodermal dysplasia	Factitious fever	Retroperitoneal fibrosis
Autonomic neuropathies	Hemoglobinopathies	Rosai-Dorfman disease
Fabry disease	Hemolytic anemias	Thrombophlebitis
Familial dysautonomia	Hypothalamic-central fever	Thyrotoxicosis, thyroiditis
Familial Hibernian fever	Infantile cortical hyperostosis	Thrombotic thrombocytopenic purpura
Familial Mediterranean fever	Metal fume fever	Venoocclusive disease
Hypertriglyceridemia	Pancreatitis	Vitamin B 12 deficiency
Ichthyosis	Parathyroid apoplexy	
other autoinflammatory diseases		
Sickle cell crisis		
Spinal cord/brain injury		

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Bartonella, Clostridium difficile, Ehrlichiosis, and Staphylococcus. Although rare, fungal infections were also noted in his study.[10]

Non-infectious inflammatory disease (NIID) conditions including autoinflammatory, autoimmune, and collagen vascular diseases are common causes of FUO. The most common causes of NIID conditions in children included juvenile idiopathic arthritis (JIA), inflammatory bowel disorders, and systemic lupus erythematosus.[7,8] Increasing relative incidence of NIID conditions causing FUO is occurring over time. It is hypothesized that better diagnostic testing has allowed more diagnosis of immune-mediated disease to be made in patients with FUO who would have previously lacked any definitive diagnosis. The true relative incidence of non-infectious inflammatory conditions is difficult to compare between studies as some separate out collagen vascular disease as a category but classify other inflammatory conditions (including inflammatory bowel diseases) with rheumatological/collagen vascular diseases. There is also debate on whether some conditions such as Kawasaki disease, Kikuchi Fujimoto, periodic fever syndromes, or monogenic autoinflammatory

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disorders would be considered as non-infections inflammatory versus "other" causes of FUO. However, the overall entire non-infectious inflammatory/autoimmune conditions are thought to make up at between 10% and 30% of FUO[6,8,10]

There is mixed evidence of changes in the relative rates of malignancy-related FUO. Although infectious etiologies are decreasing compared to other etiologies, better imaging techniques may also result in earlier diagnosis of malignancy (thereby resulting in relatively proportion decrease in malignancy-related diagnosis as well). The overall relative incidence of malignancy in children and adolescents ranged from < 5% to almost 18%.[6,8,10] However, when broken down by age, older children and adolescents made up approximately 5% of cases.[6] The most common malignancies include lymphoma (Hodgkin's and non-Hodgkin lymphoma) and leukemia. Other malignancy reported in children and adolescents include Wilms tumor, neuroblastoma, myelodysplastic syndromes,[8] and hepatocellular carcinoma.[10]

Other causes of FUO are vast. As mentioned above, some studies include multiple inflammatory or immune-mediated diseases such as Kawasaki disease (and presumably similar disease states such as multisystem inflammatory syndrome in children (MIS-C)) and Kikuchi Fujimoto (necrotizing lymphadenitis) as part of the "other" category.[7,17] However, additional etiologies include blood clots (pulmonary embolism, deep vein thrombosis or hematomas in closed spaces, central etiology (dysautonomia, diabetes insipidus, central thermoregulation issues), and hyperthyroid. Important etiology within the "other" category that need to be excluded include factitious, drug related, "habitual" hyperthermia (condition in which exam, history and minimal work up is reassuring in patients with temperatures > 100 but <101 F persistently (low grade).[18]

Fevers of unknown origin for which no cause is ever determined can range from 20% to almost 45% of pediatric cases.[6,8] As diagnosis of infections, malignancy and immune dysregulation syndromes continue to be quicker, many predict this category of "unknown" etiology may continue to grow over time.

There are significant differences is the etiology of FUO based on geography. In a recent systemic review/meta-analysis of data, etiology of FUO varied significantly depending on geographic location. The highest prevalence of infectious etiology of FUO was found in southeast Asia at 49% of their cases. Inflammatory disorders were found in approximately 20% of all cases worldwide but the highest prevalence was in the western pacific region with 34% of their cases being from inflammation conditions. Cancer was found in 15% of all studies with the highest rate (at 24%) in the eastern Mediterranean region. Similarly, "other" etiology for FUO was found in 6% of cases but up to 9% in the western Pacific region.[19,20]

The combination of local geographic exposure affecting incidence of FUO as well as the changes in diagnostic tools over time makes it difficult to isolate out or compare information in adolescents alone. Most data in adolescents comes from pediatric case reports. However, understanding adult data is also important to understand the trends from pediatric through adulthood to better understand adolescent populations.

In comparison to children 5 and under, older children and adolescents are four times more likely to have connective tissue disorder at almost 20% of all FUO. The rates of immune disorder/connective tissue disorder was especially elevated in older children and adolescents in whom fever had persisted for > 28 days.[6]

Considerations

Understanding the underlying health conditions and exposure history of patients is critical to appreciating the urgency and direction of work up for patients with FUO. As a result, patients who develop FUO can also be subdivided into categories. Traditionally,

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the vast majority of patients who developed FUO were otherwise fairly healthy. These patients are considered to have "classic" FUO. This is to separate them from three other distinct categories of "FUO." In the early 1990s, additional patient categories were proposed including health care associated fevers, neutropenic FUO, and human immunodeficiency virus (HIV)-related FUO.[2] Overtime, the categories including neutropenic and HIV related were combined with other immunocompromised state resulting in a new category of immunodeficiencies related FUO.[21] Additionally, a category of FUO in returned travelers has also been proposed.[3]

The initial criteria for neutropenic FUO included patients with an absolute neutrophil count (ANC) of less than 500 per mm3[5] or 1000 per mm3 who had fevers on multiple occasions of at least 101 F for with a negative work up for at least 3 days.[2] The overwhelming majority of FUOs in this category are thought to be from infectious etiology, even with a negative work up. Other special considerations within this category include drug-induced fevers (chemotherapy or other drug), underlying malignancy or other immune deregulatory disorder. Special emphasis of physical examination should focus on IV sites, lungs, perianal and skin folds.

As noted above, the subcategory of FUO in persons living with HIV/AIDS was proposed in 1991 (prior to the availability of retroviral therapy). However, as the risks of various etiology of FUO are likely related to underlying immune function rather than HIV itself, we recommend that patients with advanced HIV/AIDS who develop FUO be considered as one group of FUO in the immunocompromised host category.[21]

Individuals with immunocompromised states presenting with FUO can have a wide range of disease processes. This category includes patients with chemotherapy-induced neutropenia, immunosuppressant therapy for hematologic or solid organ transplantation, chronic corticosteroid use, use of biological modifying agents (eg, monoclonal antibody therapy or TNF alpha blockers), or individuals with advanced HIV with or without acquired immunodeficiency syndrome (HIV/AIDS).[21] Because of the vast degree of various risk factors, work up, and empiric treatment recommendations for people within this category, complete recommendations for this category is beyond the scope of this article. Unlike recommendations to withhold antibiotics in most "classic" FUO, patients within in category are recommend to start empiric antibiotics and antifungal therapy given the potential seriousness of infections in this population.

Criteria for health care associated FUO includes a hospitalized patient with multiple fevers of greater than 101 F (38.3 C) for at least 3 days which were not present or developing prior to admission. Work up must be negative with cultures negative for at least 48 hours.[2,5] Etiology of FUO in this cohort of patients includes health care-associated infections (eg, Clostridium difficile), post-operative complications (including deep vein thrombosis or pulmonary embolism), wound infections, line-associated infections, drug fevers and fevers from underlying disease process for which the patient is admitted.[2]

Given different exposure and potential evaluation, FUO in the returning traveler is proposed to be considered its own category. FUO in this population are felt to include more infectious processes. However, as traveling to a location will often result in the similar risks to a traveler as the local risk of endemic disease in that location, a focus on traveling should rather focus on endemic diseases in all the different locations for which a person has lived or stayed in. For providers in the US, this can include being familiar with local risk factors for various parts of the country, but also include many tropical diseases not commonly seen in the US as well as disease such as tuberculosis (TB) and other infections for which the incidence is higher in other countries. (See also Evaluation later in discussion).

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APPROACH

When patients initially present to medical attention for prolonged fevers, the initial steps should always be attempting to verify that fevers truly exist. Whenever possible, the documentation of fevers in the medical system is ideal. However, as many adolescents with FUO are otherwise healthy with outpatient evaluations, this can be more challenging. Families should be encouraged to document fevers at least twice daily using a fever diary. This can demonstrate not only the existence of fevers, but also identify frequency, severity, and any patterns of fevers.

Factitious features may be accidental (broken home thermometer, belief that reported temperatures must "add 1° to axillary temperatures"). However, history should also evaluate for the possibility of true factious fever.

A compete review of current and past history is essential in the evaluation of FUO. History should include any previous episodes of prolonged or unidentifiable fevers, preceding illnesses, and extensive exposure history (**Table 2**). Risk factors for tuberculosis exposure need to be evaluated including: exposure to individuals with TB,

Table 2
Initial Evalution

History		
Exposure	Family History	Other History
Sick Contacts	Recurrent Fever Syndromes	Local/National Travel
Animals	Unexplained or Frequent Fevers in Childhood	International Travel
International Travers	Autoimmune diseases	Weight loss
Blood products (tattoos, piercings, transfusions)	Medication	Anorexia
Contaminated Water (including wells)	Prescribed	Sexual Activity/Prevention of STD
Fresh water	Over the Counter	Immunization
Tick & Mosquito	Herbal Therapy	Medications
Others with tuberculosis	Illicit Drug Use	Recent Illnesses
Unpasteurized Foods		
Key Exam Findings		
Skin	Abdominal	Temperature
Rashes	Pain	Blood Pressure
Petechia	Organomegaly	Heart Rate
Focal abnormalities	Stool changes	Documented Weight changes
Lymphadenopathy	Musculoskeletal	Linear Growth Curve Pattern
Mucosal Changes	Joint Swelling	
Conjunctivitis	Bony Tenderness	
	Myalgia	
Minimum evaluation		
Blood culture (x2)	Chest X ray	Consider:
Urinalysis ± Urine culture		Abdominal Imaging
Complete blood count (CBC) with differential		HIV Testing
Complete metabolic panel		QuantiFERON/PPD
Peripheral Smear		
Erythrocyte Sedimentation Rate (ESR)		
C Reactive Protein (CRP)		

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chronic cough, homelessness, incarceration or institutionalization, immigration or international travelers. Additionally a patient's HIV status and home environment including previous or current history of living on a reservation or history of international travel should also be examined.[9]

A thorough physical exam is also essential. If the patient is febrile at the time of examination, vitals should be evaluated for any compensatory changes to heart rate or blood pressure. Growth curves should be evaluated for height velocity and weight gain over time. Key exam findings are also described in **Table 2**. In addition to the examination performed in the office or hospital, any history of abnormal findings (abnormal joint findings, evanescent rash, and so forth) are also important to ask about.[9]

Concerning "red flags" in the history should include unexplained weight loss, anorexia, focal symptoms, or persistent high fever. Concerning physical exam findings include organomegaly, rash, clubbing, lymphadenopathy or any focal findings.[9]

Current definition for FUO includes a minimum investigative work up without finding an identifiable cause (see **Table 2**). This includes complete blood count, metabolic panel, erythrocyte sedimentation rate, C reactive protein, and urinalysis with culture and blood cultures in addition to a chest x-ray. Although some studies indicate abdominal imaging should be included in initial evaluation, this is not part of the standard work up for pediatric patients with FUO.[13]

EVALUATION

Assuming this initial work up is negative, further work up is recommended based on clues provided by repeated examination of history and/or progression of any exam findings. Finding diagnostic clues on history, exam or labs can more than double (72% vs 30%) the chance of making a diagnosis in FUO.[14]

The fever curve itself is important for the evaluation of possible etiology. Fevers can be recurrent (fever which had resolved and then restarted), periodic (fever with a regular pattern of recurrence) or persistent.

In individuals who present with periodic or recurrent fevers ("chronic episodic fever of unknown origin"), it is important to consider periodic fever, aphthous stomatitis, pharyngitis, adenitis (PFAPA), cyclic neutropenia, or one of the several monogenetic recurrent fever syndromes. Monogenetic recurrent fever syndromes include tumor necrosis factor (TNF) receptor-associated periodic fever (TRAPS), Familiar Mediterranean Fever (FMF), cryopyrin-associated periodic fever (CAPS), mevalonate kinase deficiency (MKD, hyper IgD or HIDS).[18] Most recurrent fever syndromes present before the age of 5 and are therefore unlikely to present with new onset FUO in adolescents. However, if history suggests previous recurrent episodes for multiple years, these could be considered. Additionally, FMF and TRAPS can occasionally present later in life and should be considered in adolescents with periodic fevers of unknown etiology.[7] Fevers associated with TRAPS typically last 7 to 21 days with gaps between fever episodes lasting months to years. Associated physical exam findings include migratory myalgias with skin erythema, conjunctivitis, and periorbital edema. FMF can cause periodic fevers of 1 to 3 days duration with periods between fever episodes of weeks to years. Exam findings in FMF include rash, polyserositis, and scrotal pain (in males) or abdominal pain.[7]

Providers caring for adolescent presenting with recurrent fever must also consider a high probability of sequential limited self-resolving fevers (such as back-to-back illnesses). If history suggests exposures or symptoms of recurrent self-limiting illnesses, watchful waiting may be the most appropriate next step. If, however, the degree of

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recurrent illness seems out of proportion to local epidemiology or exposure history, providers could consider evaluation for acquired immunodeficiencies.

In adolescents with persistent FUO, a step-wise approach for the investigation of the FUO is recommended.[14] Other than chest x-ray (CXR) and blood cultures, most of the initial minimum work up is used to guide subsequent evaluation testing. Any abnormalities in initial lab work should have focused subsequent testing. Additional clues obtained by repeatedly collecting history and serial examination of patients should also guide subsequent testing.

Any patient with significant exposure history (travel, animal exposure, tick/mosquito exposure) or suggestive work up should have targeted special consideration testing (**Table 3**). Patients with abdominal findings should be evaluated for intraabdominal abscess, inflammatory bowel, cholangitis and infectious hepatitis viruses. On the other hand, patients with skin and joint manifestations may benefit from a focus on rheumatological or other inflammatory conditions (including genetic and recurrent fever syndromes). Skin manifestations such as splinter hemorrhages could suggest infective endocarditis.

Additional work up can include further immunologic evaluation, screening tests for various malignancies where available and targeting non-culture-based infectious work up (especially PCR/NAAT testing for difficult to culture infectious agents). More extensive imaging can also be considered based on focused concerns (see **Table 3**).

Care should also be taking to avoid false positives given the extensive and potentially continuing work up of fever in patients who otherwise appear well without any "red flags." As with any testing, frequent testing of low prevalent disease often result in more false positive than true positive. This can lead to unnecessary evaluation with financial and emotional implications for the patient and their family.

Imaging

At minimum, a normal CXR is a requirement for investigation prior to establishing a diagnosis of FUO. Some studies also include normal abdominal and pelvis ultrasound and/or CT abdomen and pelvis to qualify as a FUO.[13,14] In the pediatric population, many question the standard use of abdominal imaging in patients without any abdominal symptoms (abdominal pain, organomegaly, bowel changes or abnormalities on complete metabolic panel).[10] However, abdominal imaging is commonly performed as part of a later step of the approach toward FUO in both adults and pediatrics (if not performed earlier).

Additional imaging modalities could be considered based on higher suspicion of possible etiology. For example, if there is any history concerning for inflammatory bowel disease, CT or MRI enterography could be considered. Alternatively, whole-body MRI could be considered for patients suspected to have occult osteomyelitis or chronic recurrent multifocal osteomyelitis.

Multiple adults study suggest that it is cost-effective to consider an early PET CT scan in patients with FUO. PET scan can detect inflammation due to infections, noninfectious inflammatory disease and malignancies, all of which are common etiology of FUO. PET-CT has been demonstrated to be cost-effective in adult studies primarily by decreasing the length of hospital admission.[22] Even in cases where a definitive diagnosis cannot be made, using previous testing and PET-CT can result in ability to obtain a targeted biopsy site sooner allowing for more rapid diagnosis (and therefore shorter hospitalization). Although there are some studies involving the use of PET-CT in children for inflammation with or without FUO,[23] the role of PET-CT is less clear in pediatrics. In addition to the concerns of cost, radiation exposure and utility,[6] the availability of PET CT in most pediatric centers is also significantly limited.

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Table 3
Advanced work up for FUO

Initial Considerations		
QuantiFERON/TB Screen	Ferritin	Abdominal Imaging
CSF studies and culture	LDH	Echocardiogram
Stool O& P	Uric Acid	CT Abdomen/Pelvis
HIV testing	ANA	CT Chest
EBV Antibody/NAAT/PCR	Rheumatoid Factor	CT Sinus
CMV Antibody/NAAT/PCR	ds DNA	Whole Body MRI
Stool culture/NAAT/PCR	quantitative immunoglobulin levels	
Adenovirus NAAT/PCR		
Mycoplasma NAAT/PCR	Thyroid-stimulating hormone (TSH)	
	Complement - C3, C4, CH50	
	Antibody response to vaccine (titers)	
	ANCA, ASMA, ASCA, LKM	
Special Considerations		
Animal Exposures	"Travel" Related	Other Exposure
Brucella (Goats, cattle)	Malaria smear (endemic areas)	Naegleria (water)
Q fever (Sheep)	Dengue	Legionella (water)
Salmonella	Chikungunya	Toxocara (pica)
Bartonella antibodies (cats, fleas)	Hantavirus	Ticks/Mosquitos
Lymphocytic choriomeningitis (mice)	Coccidiomycosis	Lyme disease
Baylisascaris (raccoon)	Blastomycosis	Rickettsia (multiple)
Psittacosis (Birds)	Histoplasmosis	Borrelia (non-lyme)
Toxoplasmosis (Cat)	Paracoccidiomycosis	
Rat Bite Fever (rat)	Human T lymphocytic virus (HTLV)	
	Visceral Leishmaniasis	
	Cryptococcus	
Advanced Considerations		
PET - CT	Biopsy	Next-generation sequencing for infectious agents
Whole body MRI		Genome Testing panel vs whole genome vs whole exome

Abbreviaitons: ANCA, antineutrophilic cytoplasmic antibody; ASCA, anti-saccharomyces cerevisiae antibody; ASMA, anti-smooth muscle antibody; CT, computerized tomography; MRI, magnetic resonance imaging; NAAT–nucleic acid amplification testing; PCR, polymerase chain reaction.

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OUTCOMES

Outcomes related to FUO are typically correlated to the outcomes associated with the underlying etiology found. Older articles have reported 6% to 9% mortality rate in pediatric FUO. More recent publications in pediatrics suggest overall good prognosis in almost all patients with FUO.

Interestingly, one studying looking at long-term follow-up in adults with FUO did demonstrate a slightly higher incidence of malignancy for up to a year post-FUO (not diagnosed during the FUO evaluation). This was primarily due to increased rates of Hodgkin's lymphoma and non-Hodgkin's lymphoma as well as myelodysplastic/

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myeloproliferative disorders.[24] Limited follow-up studies in pediatrics demonstrate that most recover without sequela, although there are a few cases later diagnosed with JIA or other causes of their previous FUO (such as recurrent intussusception) when followed for several years after FUO episode.[25] Another follow-up study in pediatrics demonstrates some patients will go on to develop a diagnosis of autoimmune or inflammatory disorders (such as uveitis, Crohn's).[26]

FUTURE DIRECTIONS

Current technology has dramatically changed the dynamic of FUO over the past 100 years. As more, faster, cheaper, and better diagnostic technology continues to become available, more etiologies that would have otherwise been undiagnosable FUO will be recognized. On the other hand, more rapid diagnosis may further decrease the total incidence of FUO in the future, as fewer patients will have persistentent fevers for 2 or 3 weeks without an identifiable cause. However, to be able to follow changes over time, diagnostic criteria will need to be consistent, and studies will need to be conducted to determine the true incidence of FUO in the general population (or in the various FUO subset populations).

Already, tertiary centers and research studies are using advanced technology to diagnose infections and genetic autoimmune/inflammatory conditions which could present at FUO. Next generations sequencing of human plasma looking for infectious DNA is commercially available in the US and other parts of the world. This can potentially detect more infectious processes which would be responsible for FUO.[27]

Genomic sequencing is already being used to diagnosis monogenic autoimmune periodic fever syndromes. Additional genetic tests are likely to be discovered for more NIID processes in the future. Genome sequencing has been used to identify host factors related to fevers. FUO are often called uncommon presentations of common diseases. One study examined whole exome genome in 15 cases of FUO in China (seven later found to have infectious causes). Some were found to have genetic predisposition for infectious risk (GATA 2, CFTR mutation) with almost half the cases mentioning a genetic variant of uncertain significance in genes of interest related to fever pathway or risk factors for infectious disease.[28] This novel approach to identifying human host pathways may explain why common diseases are presenting in an uncommon fashion is intriguing, but care must be taken to minimize overinterpretation, especially in variants of uncertain significance.

Metabolomics refers to the study patterns of small molecule metabolites (lipids, sugars, amino acids, and so forth) to determine what causes those small molecule patterns. This can be analyzed using nuclear magnetic resonance (NMR) spectroscopy or mass spectroscopy. Commercially available products already exist to identify the name of microbial growth on plates in microbiology labs. However, metabolomics may be used increasing in patient-derived samples. Research studies have demonstrated the ability to detect infectious pathogen signs in hosts.[29] However, like other developing technologies, care in interpretation must be used as previously identified "signals" of infection were later identified to be non-specific inflammatory signals rather than unique targets to specific infectious disease processes.

Many of these developing technologies are currently expensive and of uncertain significance in FUO. However, it is possible that with further study and more cost-effective models, one or several of these may become of use in FUO in the future. More rigorous study would need to be conducted to ensure these more broad range "shot gun" approaches to FUO do not yield more incidental positive results which are not related to the patient's actual condition.

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DISCUSSION

Better culture and non-culture techniques (eg NAAT/PCR) for infectious etiology, improved imaging (CT, MRI, PET) and more, faster available testing for non-infectious immunologic disorders has dramatically changed the nature of FUO work up since it was first recognized over 100 years ago. Despite this, fever of unknown origin remains a diagnostic dilemma for many providers. With significant variation in the incidence of etiology of FUO throughout the world and limited data in the US, it can be challenging to fully appreciate the etiology of FUO in adolescents within the US.

Although rates of infectious etiology for FUO may be decreasing, this still appears to account for the largest percentage of FUOs for which an identifiable cause is found in both children and adults. Adolescents do have increasing connective tissue and other NIID etiology at higher rates than general pediatric populations. Despite advances in technology, a large percentage of FUO remain without identifiable etiology even after fevers resolve.

SUMMARY

Fevers of unknown origin (FUO) remain a diagnostic dilemma. The differential remains broad with etiology most commonly including infectious, autoimmune, and malignant related. A significant portion of adolescents with FUO may never have an identifiable etiology found. However, the prognosis of FUO without determined etiology and in the absence of "red flag" symptoms is overall reassuring.

CLINICS CARE POINTS

- To be considered a FUO, a fever should be present for > 14 to 21 days with negative/reassuring exam and lab evaluation including CBC with differential, complete metabolic panel, urinalysis, urine and blood culture, ESR, CRP, CXR.
- In clinical practice, more rapid investigation for prolonged fevers is often started by 7 days into fever
- Fever history should differentiate between recurrent, periodic, and persistent fever
- Extensive exposure history and serial physical exams are important steps toward a targeted approach to work up classic FUO
- While over 200 possible etiology exist, patients with FUO often go undiagnosed.
- Prognosis is generally favorable in patients with FUO without "red flag" symptoms, especially in those without identifiable etiology after work up

DISCLOSURE

The author has no disclosures.

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